CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

MONOCROTOPHOS (AZODRIN)

SB 950-095, Tolerance # 296

December 5, 1986
Revised April 2, 1987; January 8, 1988
Revised July 7, 1988

I. DATA GAP STATUS

Combined (chronic + onco) rat: No data gap, no adverse effect

Chronic dog: No data gap, no adverse effect

Onco mouse: No data gap, possible adverse effect (not onco)

Repro rat: No data gap, possible adverse effect

Terato rat: No data gap, no adverse effect

Terato rabbit: No data gap, no adverse effect

Gene mutation: No data gap, possible adverse effect

Chromosome: No data gap, possible adverse effect

DNA damage: No data gap, possible adverse effect

Neurotox: No data gap, no adverse effect

Note, Toxicology one-liners are attached

** indicates acceptable study;

Bold face indicates possible adverse effect.

Summary and previous revisions prepared by J.Gee; revised 1/8/88 by M.Harnois; revised July 7, 1988 by J. Gee.

II. TOXICOLOGY SUMMARY

COMBINED RAT

** 023 to 027 31654 to -59 "A Long-term Feeding Study with Azodrin in Rats to Investigate Chronic Toxicity and Oncogenicity (6, 12, 18 and 24 Month Necropsies.)" (Sittingbourne Research Centre, SBGR.82.062, 3/83) Monocrotophos (Batch no. 8-28-0-0, 78.7% E-isomer, 5.7% Z-isomer, possibly 12 other components), fed in the diet for 2 years to Wistar rats, 85/sex/test group and 170/sex in controls at 0, 0.01, 0.03, 0.1, 1.0 or 10.0 ppm (nominal). Initial review noted that the study was acceptable with remarkable findings as lipophage aggregates in the lung and a possible increase in pituitary tumors in females at 10 ppm (Gee, 11/12/85). A re-examination was made of the documents on file, especially those related to historical controls and dosage (033 48748-49). The re-examination found that previously noted effects were not biologically significant. Systemic NOEL (nom.) = 1.0 ppm (slight persistent decreased body weight in males); oncogenic NOEL (nom.) $\geq$10 ppm. Cholinesterase NOEL = 0.03 ppm. **No adverse effect; acceptable**. (Harnois, 1/6/88, Gee, 11/12/85 and 7/7/88) EPA 1-liner: Supplementary. Systemic NOEL = 0.883 ppm, ChE NOEL = 0.026 ppm. Carcinogenic potential not determined pending the submission of historical control data. [See document 296-033, Record # 48749 for these data. EPA now grades the study as "minimum".]

033 48748 Supplement to 31654-59 consisting of EPA's comments and corrections prepared in 1984 and a 2-page Memorandum dated May 24, 1985, in which the conclusions on 6 studies are given. The 2-year rat study is "Minimum". Gee, 4/2/87.

033 48749 Supplement to 31654-59 consisting of historical control data from three experiments (no dates) for pituitary neoplasms. From the data given, with a high of 93.4% in decedent females, the biological significance of the incidence in the high dose females in the above study is in doubt, as discussed in the actual report. Gee, 4/2/87.

CHRONIC RAT

006 1145 Summary of 31654 - 59 reviewed under Rat, Combined, above. No data.

001 020972 (No lab, 1967) Summary of a study in rats, 25/sex/group, fed 0, 1, 10 or 100 ppm for 2 years. No data. Study said to be invalid and a replacement study initiated in 1978 (see above). J. Christopher, 5/24/85.

033 48750 Summary of 20972, study done at Woodard, 1967.

CHRONIC DOG

** 022 36153 "Azodrin Safety Evaluation by a Chronic Feeding Study in the Dog for Two Years - Final Report." (Woodard Res. Corp., 7/10/67) Monocrotophos (Code 7-3-4-16; 83% alpha isomer, 7% beta isomer, 4% DMMD); fed to 4/sex in controls, 3/sex at 0.16, 1.6 or 16 ppm for 2 years and 2/sex at 100 ppm, for 1 year; Cholinesterase NOEL = 1.6 ppm, nominal systemic NOEL = 16 ppm (salivation, soft stools and tremors); no histopathology findings reported. **No adverse effect reported**. Initially reviewed as unacceptable due to missing data (no individual clinical observations, stability problem in diet until storage conditions changed, no summary data, dose selection.) The study was upgraded to **acceptable** following the submission of supplemental data in Document 296-034, Record # 50450, consisting of individual data and summary tables. The study has some flaws by 1982 guidelines but contains sufficient data to determine that at the high doses, no chronic effect occurred other than cholinesterase inhibition. J. Gee, 11/8/85 and 4/2/87.
EPA 1-liner: Minimum. ChE NOEL = 1.6 ppm, systemic NOEL = 16 ppm (salivation and tremors).

034 50450 Supplement to 36153.

001 020973 Summary of 36153.

033 48750 Summary of 36153.

ONCOGENICITY, RAT

See under Combined Rat above.

ONCOGENICITY, MOUSE

**** 011 to 017 019973 to 019978** "Two Year Oncogenicity Study in Mice Fed Azodrin." (Shell Tox. Lab., London, 10/19/82). Monocrotophos (Batch 8-28-0-0; 78.7% E-isomer), fed in the diet at 0, 1, 2, 5 or 10 ppm to CD mice for 104 weeks, 77/sex/test group and 154/sex in control group. Initial review found 80% inhibition in plasma cholinesterase at high dose; plasma, brain and RBC cholinesterase depressed at all levels; dose-related increase in convulsions; cholinesterase NOEL < 1 ppm; no oncogenicity; acceptable with minor variations. (J. P. Christopher, 5/30/85). A review of additional information (039 57703) confirmed the seizures as an adverse effect (increased numbers of animals affected; increased number of seizures/animal). Systemic NOEL <1 ppm for increased frequency of females with seizures; NOEL = 2 ppm for frequency of seizures in males; **acceptable**. (Harnois, 12/21/87 and Gee, 7/7/88)

EPA 1-liner (from 48748 in 033): Supplementary. Not oncogenic at 10 ppm (HDT). Strain of mouse not specified. [Shell has submitted additional data to EPA but the nature of these is not described.]

039 57703 Addendum to 011 019973 ff. EPA review comments and Registrant response. Identifies mice as Crl:CD(R)-1 (ICR)BR strain; cites references for spontaneous tumors. Respondent suggests that observations reported as convulsions were "fright induced seizures" rather than whole body contractions, gives frequency in controls of a comparable study as 18.3% for males and 3.0% for females and notes that the life-span of mice in 019973 was not decreased by the seizures. However, the dose-effect indicates that the frequency was related to the test substance. Respondent's comments indicate that retinopathy and lenticular degeneration were not related to treatment, but there are insufficient data in the report for an evaluation since most animals selected for this exam died before 2 years. (Harnois, 12/21/87)

REPRODUCTION, RAT

**** 028 36161 to -63** "A Reproduction Study in Rats Fed Azodrin." (Sittingbourne Res. Centre, SBGR.81.143, 11/81) Monocrotophos, Batch 8-28-0-0, 78.7% E-isomer, 5.7% Z-isomer, 0.2% trimethylphosphate plus 12 other components; fed in the diet to Wistar rats at 0, 0.1, 1, 3 or 10 ppm, 2 generations, 1 litter/generation; 13 males and 25-26 females per group; diets were prepared and analyzed weekly; used if ± 10% of nominal; loss of 6%/day in cage; food changed every 3-4 days; reproduction NOEL = 1 ppm (increased pre-weaning loss, "poor mammary development" in a few F0 and F1 dams at 10 ppm and f1 females at 3 ppm), systemic parental NOEL = 3 ppm nominal (lower body weight, smaller fecal pellets). Possible adverse effect on reproduction in the absence of significant parental toxicity. **Acceptable.** Gee, 11/13/85.
EPA 1-liner (from 48748 in 033): Minimum. NOEL (reproductive, parental, off-spring) = 2.7 ppm (decreased fertility, pup viability/weight, and lactation).

017 1147 Summary of 36161 - 63 above.

033 48751 Data Evaluation Record of EPA on 36161 - 63. Evaluated as core minimum with the following comments on deficiencies: Lack of food consumption (not required by 1982 USEPA Guidelines) precludes determination of intake, poor stability in diet meant actual concentration was an average of 13% lower than nominal, no data for the preliminary study upon which dose selection was based, no description of how the 5 male and female pups were selected for histopathology, once daily observation was too infrequent allowing for cannibalization and/or autolysis and preventing determination of the length of gestation less than the nearest day (important in that this parameter appeared to be increased in time in the high dose), deficiency in vitamin K in the diet early in study and some statistical analyses and calculations were not performed. The conclusion, however, was that none of these was sufficient to cause the study to be rejected.

Pathology exam noted involuted mammary tissue apparently nonsecretory in the 3 high dose and one 3 ppm females whose litters apparently starved to death. Also, some liver changes were noted in weight and in histopathological exam.

EPA agrees that the body weight in the high dose males was affected by the test compound. Sufficiently high dose (10 ppm) was used with the signs of toxicity including increased incidence of abnormal fecal pellets at 10 and 3 ppm, body weight changes, pup mortality and reproductive effects. The reproductive effects were poorly developed teats, lactation problems, decreased viability and lactation indices. Gee, 12/5/86.

001 020970 Summary of a 3-generation reproduction study in 10 males/20 females per group tested at 2, 5, 12 or 30 ppm in feed. No data but report states decreased litter weights at 12 and 30 ppm, stunting at 12 and 30, NOEL stated as 2 ppm. **Unacceptable**. J. Christopher, 5/24/85.
EPA 1-liner: Minimum. Reproduction NOEL = 2 ppm. Study identified as conducted at Hine, 3/66.

TERATOGENICITY, RAT

** 010 019972 "Technical AZODRIN (SD 9129) Teratology Study in SD CD Rats" (Toxigenics, Inc., 12/8/83) Monocrotophos (55F, 79% E isomer) was given by oral gavage at 0, 0.3, 1.0 or 2.0 mg/kg/day to mated female Sprague Dawley rats (26/ group) on days 6-15 of gestation. Maternal NOEL = 0.3 mg/kg/day (decrease in body weight); developmental NOEL = 1.0 ppm (decreased length and weight, increased unossified sternebrae). Initial review (J. P. Christopher, 5/28/85) found no adverse effect since no developmental effects noted in absence of maternal effect; report unacceptable but upgradeable with submission of analytical results on dosing solutions. Documents 033 48753 and 039 57702 contain data showing adequate concentration and stability under test conditions. (Harnois, 12/28/87) Upgraded to **acceptable** upon reconsideration that the technical material was adequately described - see 296-001. (Gee, 7/7/88)

033 48753 and 039 57702 Addenda to 010 19972. Analysis of material used in the study showed it to be 79% E isomer, but the composition of approx. 12% of the material remains unknown; analyses of the dosing preparation showed nominal concentrations were closely approximated during the dosing period. (Harnois, 12/18/87)

033 48752 Review of rat teratology study (019972) by EPA. Conclusion is that monocrotophos is not teratogenic at the HDT and the study is CORE minimum. There is no discussion of study deficiencies. Gee, 12/5/86.

TERATOGENICITY, RABBIT

** 037 54478 "Developmental toxicity study of Azodrin Insecticide (Technical) in New Zealand White (NZW) Rabbits." (Argus Research, 1/12/87) Azodrin Technical (75%; Batch 13-4-0-0) in water was administered at 0, 0.1, 1, 3 or 6 mg/kg/day to artificially inseminated females on gestation days 6 through 18. 13 deaths in the 6 mg/kg/day group, and 1 death in the 3 mg/kg/day group. Maternal NOEL = 1 mg/kg/day (mortality, early delivery, clinical observations), dev. tox. NOEL = 3 mg/kg/day (increased resorptions) No adverse effects since no developmental toxicity without maternal toxicity; found unacceptable but upgradeable with submission of analyses of dosing solutions. (Gee, 4/2/87). Additional data were reviewed: historical information on lung agenesis (040 60522) indicated that frequencies observed in the 3 and 6 mg/kg/day groups were within the control range; information on purity and the results of dosing preparation analysis were submitted (039 57704), indicating that nominal concentrations were approximated during treatment. Unacceptable but upgradeable (composition of the test substance is needed). (Harnois, 12/18/87) Review of data in 296-001 indicates that the technical material used in the study had a composition close to the usual product. Study upgraded to **acceptable** status. (Gee, 7/7/88)

039 57704 Addendum to 037 54478. The test substance was identified as from batch 13-4-0-0, and stated to be 75% pure. No additional information on composition of this batch was given. The prepared dosing solutions contained the substance in essentially nominal amounts; the concentrations of stored samples were not appreciably changed during the period of dosing. (Harnois, 12/18/87)

040 60522 Historical control data for 037 54478. EPA reviewer noted frequency of agenesis of the diaphragmatic lobe of the lung to be increased at 3 and 6 mg/kg/day; data show the background frequency at the testing facility has increased and the frequencies at 3 and 6 mg/kg/day to be within control range; an Argus representative reported that the effect was due to genetic drift in the breeding stock (Hazleton/Dutchland). (Harnois, 12/18/87)

028 36160 "Toxicity Studies with Azodrin: Teratology Experiment in Rabbits Given Azodrin Orally." (Tunstall Lab, 10/72) Monocrotophos technical, 40% w/v in hexylene glycol given in gelatin capsules at 0, 0.7 or 2 mg/kg, days 6 - 18; 32 in vehicle control, 16 in each test group with thalidomide as positive control; unclear whether the dose is based on the a.i. or technical grade Azodrin; maternal NOEL = 0.7 mg/kg (weight gain), developmental NOEL > 2 mg/kg. No adverse effect reported; **unacceptable** (no individual data, unclear dose levels; only 1/3 for visceral and 2/3 for skeletal - all fetuses should be examined for both; dose selection - report states 2 mg/kg the MTD based on a preliminary study but no data is presented - only marginal effect on body weight was noted in this study.) Gee, 11/13/85. EPA 1-liner: Minimum. Teratogenic NOEL > 2 mg/kg/day; fetal toxicity NOEL > 2 mg/kg/day; maternal toxicity NOEL > 2 mg/kg/day.

001 952472 Summary of 36160.

MUTAGENICITY, GNMU

Microbial Systems

029 38547 "Toxicity Studies with Azodrin. Effect of Azodrin on Microorganisms in the Host-mediated Assay and in Vitro." (Turnstall Lab, 7/74) Serratia marcescens and Salmonella typhimurium strains TA1535, TA1536, TA1537 and TA1538, with technical grade

Azodrin, 77.3%, by plate incorporation. Report states results were Negative. No data. **Unacceptable**. Gee, 11/8/85.

029 36164 "The Mutagenic Effect of Organophosphate Insecticides on Escherichia coli." (Tunstall Lab, 8/71) Monocrotophos as 24% solution, w/v, tested with Escherichia coli B/r WP2 strain in a screening of 9 pesticides; added on a filter disk, in triplicate. No adverse effect reported. **Unacceptable** (no data given). Gee, 11/8/85.

001 021435 Summary of a report on the Ames assay in Salmonella with no data. Unacceptable. Also included Escherichia coli with no data.

033 48755 "In vitro and In vivo Mutagenicity Studies of Environmental Chemicals." (SRI International, 1/84) Salmonella; monocrotophos, no purity stated; strains TA98, TA100 and TA1535, 1 plate per concentration, 3 trials at 0, 500, 1000, 2000, 3000, 4000 or 5000 ug/plate ± S9 (trials 1 and 2) or 1000, 2500, 5000, 7500, 10,000 or 20,000 ug/plate ± S9 (trial 3); concentration-dependent increase in revertants in TA100 ± S9; **Unacceptable**, possibly upgradeable (no description of methods, 3 of 4 recommended strains, no description of test article, single plate per concentration.) Gee, 12/3/86.

033 48765 "In vitro and In vivo Studies of Selected Pesticides to Evaluate their Potential as Chemical Mutagens: In vitro Assays with Salmonella and E. coli." (SRI, Menlo Park, 11/13/75) Summary. Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 ± rat liver S9. Negative results stated. No data. Also, Escherichia coli WP2. Gee, 12/4/86.

Mammalian and Other Systems

033 48758 "In vitro and In vivo Mutagenicity Studies of Environmental Chemicals." (SRI International, 1/84) Mouse lymphoma L5178Y; monocrotophos, no purity stated; tested -S9, 0 to 900 ug/ml, 10 concentrations, +S9, 0 to 1200 ug/ml, 10 concentrations, based on toxicity, duplicate cultures; includes a preliminary study; increased mutant colonies with and without S9; **unacceptable** but upgradeable (no material and methods section, no description of test article.) Gee, 12/2/86.

036 51511 "Drosophila Mutagenesis Tests." (WARF, approximately 1976, R. Valencia) Twenty chemicals were tested for sex-linked recessive lethal effects at 0.1 to 4 ppm; CS/Y males crossed with FM6/FM6 females for P1 cross; no adverse effect reported; no data. **Unacceptable**. Gee, 4/1/87

SUMMARY: No one study as submitted is adequate to fill the data requirement but several could possibly be upgraded if missing information is submitted. Collectively, the reports provide sufficient evidence that monocrotophos is mutagenic both in bacteria and in mammalian cells and the data gap is considered filled with a possible adverse effect for genotoxicity. Gee, 4/2/87.

MUTAGENICITY, CHROMOSOME

029 36166 "Toxicity Studies on Azodrin: Dominant Lethal Assay in Male Mice after a Single Oral Dose of Azodrin." (Turnstall Lab, 9/73) Monocrotophos, >99%, Batch TSL/62/70/P; given in a single oral dose at 0, 1, 2 or 4 mg/kg to 12 males per group; mated 1:3 per week for 8 weeks; no toxic effects reported; NOEL > 4 mg/kg; **unacceptable** (no positive control; pregnancy rate of 60-80% resulted in fewer pregnant females than recommended; no justification of dose and no evidence MTD was approached; no individual data; not clear if given by gavage.) Gee, 11/12/85.
EPA 1-liner: Minimum. NOEL > 4 mg/kg (HDT).

036 51512 "Mammalian Screens." (SRI, no date) Ten pesticides were tested for dominant lethal effect in mice following feeding to males for 7 weeks. No adverse effects reported; no data for monocrotophos. **Unacceptable**. Gee, 4/1/87

001 1142 Summary of 36166.

033 48763 Summary of 36166.

033 48768 "In vitro and In vivo Studies of Selected Pesticides to Evaluate their Potential as Chemical Mutagens: Dominant Lethal Test with Azodrin in Mice." (SRI, Menlo Park, 11/13/75). Fed in the diet to ICR/SIM male mice for 8 weeks at 0, 15, 30 or 60

mg/kg; TEM as positive control; mated 1:2 for 7 days for 8 weekly periods. No data. Stated to be negative. Incomplete and **Unacceptable**. Summary only. Need full study. Gee, 12/4/86.

029 36167 "Toxicity Studies with Azodrin: Chromosome Studies on Bone Marrow Cells of Mice After a Single Oral Dose of Azodrin." (Turnstall Lab, 6/73). Monocrotophos, analytical grade, > 99%, Batch TSL/62/70/P, given in a single oral dose (by gavage?) to 8/sex/group at 0, 2 or 4 mg/kg to CF1 mice; sacrificed 4/sex/group at 8 and 24 hours after dosing; scored 100 cells per animal; no adverse effect on chromosomes or on animals is reported; NOEL > 4 mg/kg; **unacceptable** (inadequate high dose although selection was based on 1/4 and 1/2 the LD50, no positive control, no individual data, use of analytical rather than technical grade.) Gee, 11/12/85.
EPA 1-liner: No grade. NOEL > 4 mg/kg (HDT).

001, 6 and 17 021437 Summary of 36167.

033 48762 Summary of 36167.

033 48760 "In vitro and In vivo Mutagenicity Studies of Environmental Chemicals." (SRI International, 1/84) Micronucleus test; monocrotophos, no purity stated, given to 24/group (no sex or species indicated) at 0, 2, 4 or 8 mg/kg twice at 24-hour interval; sacrifice at 48, 72 and 96 hours; PCE/RBC ratios were not altered by treatment; no increase in micronuclei. TMP as positive control. **Unacceptable** (missing methods section, dose selection too low, no description of test article, no indication of number of cells scored.) Gee, 12/4/86.

036 51510 "Micronucleus Test on Monocrotophos." (SRI International, 1/10/80) Azodrin (lot no 9-SCL-77; no purity) given twice by i.p. injection at 0, 2, 4 or 8 mg/kg to 8 males (no females) per group per sacrifice time; sacrifices at 48, 72 or 96 hours after the first injection; 500 polychromatic erythrocytes scored per animal; some fluctuation in mean

PCE/RBC with the mean for the high dose being slightly lower at all three sacrifice times; no mortality; **unacceptable** (no MTD used and use of males only without justification); no adverse effect reported. Report states that study meets all criteria "...except that of maximum tolerated dose." Further, the report states that the result should be confirmed by testing at a dose where some fatalities occur. This report contains the same data as in 48760. Gee, 4/1/87

033 48757 "In vitro and In vivo Mutagenicity Studies of Environmental Chemicals." (SRI International, 1/84) In vitro sister chromatid exchange in CHO cells, monocrotophos, no purity stated, ± S9 at 0, 0.0125, 0.025, 0.05, 0.1 or 0.2% for 2 hours with activation, at 0, 0.0025, 0.005, 0.01, 0.02 or 0.04% without activation. **Unacceptable** (missing material and methods section, no purity of test article), possibly upgradeable. Increase in sister chromatid exchanges with and without activation. Gee, 12/3/86.

SUMMARY: No one study as submitted is adequate to fulfill the data requirement but several might be upgraded if the complete reports were submitted. While the tests for gross chromosomal change (dominant lethal, micronucleus) appear to be negative, the positive SCE test indicated that changes within chromosomes may have been induced both with and without activation. The data gap is considered filled collectively by the studies submitted, with indications of a possible adverse genotoxic effect. Gee, 4/2/87.

MUTAGENICITY, DNA/OTHER

029 36165 "Toxicity Studies with Azodrin." Effect of Azodrin on Microorganisms in the Host-Mediated Assay and In Vitro. (Turnstall Lab, 7/74) JR(G), 11/12/85. Saccharomyces cerevisiae D4; monocrotophos technical, 77.3% w/v in hexylene glycol and analytical grade > 99%; CF1 male mice, 2/dose, were injected i.p. at 0, 4, 8, 12 mg/kg or at

2 and 4 mg/kg in repeat trial; yeast was injected i.p. immediately after dosing and the animals sacrificed at 5 hours; 4 plates each for tryptophan and for adenine revertants; for in vitro assay, both technical and analytical were used - technical at 0, 25, 39 or 50 mg/ml and analytical at 4, 5, 8, 10 or 50 mg/ml; adverse effect seen as increase in mitotic gene conversion loci in concentration-related manner; **unacceptable** (activation was not included in the in vitro assay for comparison, no individual plate counts.) Gee, 11/12/85.
EPA 1-liner: Minimum. Mutagen in Saccharomyces. Not a mutagen in Ser. marcescens or Sal. typhimurium. Weak mutagen detectable only at high conc. (5-50 mg/ml) in extremely sensitive system.

001 021436 Summary of 36165.

033 48764 Summary of 36165. Increase in gene conversion.

033 48761 Summary of host-mediated section of 36165. No adverse effect reported.

033 48766 "In vitro and In vivo Studies of Selected Pesticides to Evaluate their Potential as Chemical Mutagens: Mitotic Recombination in Saccharomyces." (SRI, Menlo Park, 11/13/75.) Saccharomyces D3 showed an

increase in mitotic recombination without activation needed. No data. Escherichia coli P3478 and W3110 were negative for growth differential - no data. Bacillus subtilis M45 and H17, rec+/-, also were negative - no data. Gee, 12/4/86.

033 48756 "In vitro and In vivo Mutagenicity Studies of Environmental Chemicals." (SRI International, 1/84) Saccharomyces, monocrotophos, no purity stated; strain D3 (1 trial) and strain D7 (2 trials) ± S9 at 0 to 5% w/v for D3 and 0 to 3% w/v for D7; adverse effect seen as a concentration-dependent increase in mitotic recombinants, gene conversion and reverse mutation; Salmonella rec+/- strains at 5 and 10 ul (concentration no given) showed differential growth in two trials; Salmonella uvrB +/- strains did not show differential growth. **Unacceptable** but possibly upgradeable with submission of the full report. No materials and methods are included, no purity of the test article. Gee, 12/3/86.

001 021595 Summary of a study using Saccharomyces cerevisiae. Tested at 8 and 50 mg/ml with no data. Summary states "Azodrin at high concentrations can produce lethal and mutagenic effects."

033 48759 "In vitro and In vivo Mutagenicity Studies of Environmental Chemicals." (SRI International, 1/84) Unscheduled DNA synthesis in WI-38 cells; monocrotophos, no purity stated; ± S9 at 0, 1.2, 3.7, 11.1, 33.3 or 100 x 10^{-4} M, 6 replicates; 2 trials -S9, 1 trial +S9; positive effect with increase in DPM/ug DNA +S9; **Unacceptable** (missing materials and methods, no purity of test article), possibly upgradeable. Gee, 12/3/86.

033 48771 "Unscheduled DNA Synthesis Testing for Substitute Pesticides." A. Mitchell, SRI, author. Excerpt from "Substitute Chemical Program - The First Year of Progress. Proceedings from a Symposium, Vol. II. Toxicological Methods and Genetic Effects Workshop." Pages 151-153. Unscheduled DNA synthesis in WI-38 which were exposed for 3 hours -S9 and 1 hour +S9; measured incorporation of ^{3}H-thymidine in DNA by liquid scintillation. Azodrin positive ± S9. **Unacceptable;** no data. May be same as 48759. Gee, 12/4/86.

033 48767 "In vitro and In vivo Studies of Selected Pesticides to Evaluate their Potential as Chemical Mutagens: Unscheduled DNA Synthesis Testing." (SRI, 11/13/75) Monocrotophos, no purity stated, with WI-38, incubated 3 hours -S9, 1 hour +S9, mouse liver to activate. Increase in incorporation of radioactive thymidine ± S9. **Unacceptable,** no data. [Possibly same study as 48759.] Gee, 12/4/86.

SUMMARY: No one study as submitted is adequate to fill the data requirement but several might be upgraded with the submission of the missing information. Collectively, the studies indicate positive genotoxic effects in studies with several different endpoints, namely mitotic gene conversion and mitotic recombination in yeast and unscheduled DNA synthesis in mammalian cells. Gee, 4/2/87.

MISCELLANEOUS GENOTOXICITY STUDIES

001 021439 Summary of toxicity data indicating adverse genotoxic effects in a number of areas such as mitotic recombination, mutation, unscheduled DNA synthesis, sister chromatid exchange.

NEUROTOXICITY

029 36169 "Neurotoxicity Evaluation of Azodrin Insecticide: Subchronic Oral Administration in Hens." (Food and Drug Res. Lab., 6/22/81) Monocrotophos, 77.4%, given in gelatin capsules to 10 hens per group for 96 days at 0, 0.03, 0.1 or 0.3/0.5 mg/kg (dose raised on day 78); capsules were prepared daily; TOCP as positive control and an untreated as well as vehicle control group; plasma cholinesterase measured on days 1, 30, 58 and at sacrifice; histopathology on nerves of all animals; cholinesterase NOEL < 0.03%, NOEL (other) > 0.3%; **unacceptable** (not an acute delayed neurotoxicity study). Neurotoxic esterase inhibited in TOCP but not with monocrotophos. No adverse effect. Gee, 11/12/85.
EPA 1-liner: Minimum. Egg production NOEL = 0.1 mg/kg, neurological clinical score = 0, ChE plasma NOEL = 0.03 mg/kg.

001 952468 Summary of 36169.

008 1169 Rangefinding study for 36169. (Food and Drug Research Labs, 6/22/81) Monocrotophos given in gelatin capsules to 5 hens per group at 0, 0.03, 0.1, 0.3, or 1.0 mg/kg for 14 days. No data. **Unacceptable**. Christopher, 5/24/85.

028 36168 Rangefinding study for 36169 (same test as in 1169). Reviewed with 36169. 0.3 and 1 mg/kg inhibited brain cholinesterase; severe acute clinical signs in those given 1 mg/kg resulted in sacrifice of animals in this group.

033 48754 EPA evaluations of 1169 and 36169 neurotoxicity studies. Range-finding study called adequate as that type of study with egg production NOEL = 0.03 mg/kg, plasma cholinesterase NOEL = 0.03 mg/kg. For subchronic, 90-day study, the egg production NOEL = 0.1 mg/kg/day and no neurotoxicity was exhibited at 0.3 mg/kg b. wt. Grade CORE minimum. Gee, 9/2/86.

001 952466 Summary with no data. Hens (number not stated) were given a single oral dose of Azodrin at 6.7 mg/kg stated to be the LD50. Dose was repeated at 21 days. Unacceptable. EPA 1-liner: Supplementary. NOEL = 6.7 mg/kg (only level tested), Tunstall, 5/78.

Summary: In view of the negative findings in the 14-day (rangefinding) and 96-day studies, there is no deficiency in this area.